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Prognostic Value of Serum Tumor Markers in Patients With Stage III NSCLC Treated With Chemoradiotherapy

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Abstract. *Background/Aim: Serum tumor markers such as carcinoembryonic antigen and cytokeratin subunit 19 fragment are generally monitored in non-small cell lung cancer (NSCLC) patients in the clinical practice. However, their clinical relevance in stage III NSCLC treated with concurrent chemoradiotherapy (CCRT) remains unclear. Herein, we examined the clinical relevance of tumor markers in those patients. Patients and Methods: We retrospectively reviewed 62 consecutive patients with stage III NSCLC who received CCRT. We examined the associations of tumor marker levels with their prognosis. Results: There was no correlation between pretreatment tumor marker levels and prognosis. Normal tumor marker levels post-CCRT were significantly associated with favorable progression-free survival (54.8 versus 14.5 months, p=0.02) and overall survival (71.7 versus 40.4 months, p=0.06) compared with high tumor marker levels post-CCRT. Conclusion: We revealed that normal tumor markers levels post-CCRT in stage III NSCLC might be a useful surrogate marker for curing those patients.*

Lung cancer is the leading cause of cancer-related death worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases and approximately 30% of NSCLC patients present with stage III disease (2-3). Concurrent chemoradiotherapy (CCRT) is the standard of care for these patients (4-5). Despite extensive research into the treatment of NSCLC, the prognosis of patients with stage III disease remains poor, with a median survival of approximately 20 months (6-8).

Several researchers have investigated the predictive value of ^{18}F-fluorodeoxyglucose uptake on positron emission tomography, tumor volume, and clinical tumor response in patients with stage III NSCLC treated with CCRT (9-15). However, these studies were unable to clarify the predictive value of these factors because of various heterogeneities in the tumors and among patients with stage III NSCLC.

Serum tumor biomarkers, such as carcinoembryonic antigen (CEA) and cytokeratin subunit 19 fragment (CYFRA) are generally used to evaluate NSCLC in clinical practice in Japan. However, their clinical relevance in stage III NSCLC remains unclear. Therefore, in the present study, we investigated the associations between tumor markers and clinical outcomes.

Patients and Methods

Patients. We retrospectively screened consecutive patients who had been diagnosed with stage III NSCLC at the Kurume University Hospital, Japan, between 2009 and 2014. Patients who had been diagnosed pathologically with NSCLC had received CCRT with platinum-containing chemotherapy and underwent tumor marker testing, before treatment or at CCRT completion were eligible for inclusion. The present study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Boards of Kurume University Hospital.

Statistical analyses. We evaluated the parameters associated with the survival of patients with stage III NSCLC who had received CCRT. We assessed tumor shrinkage according to the response evaluation criteria in solid tumours (version 1.1) (16). We analyzed the associations of pretreatment levels of serum CEA and CYFRA with progression-free survival (PFS) and overall survival (OS) using Pearson's chi-squared test. PFS was defined from the date of initiation of first-line treatment to the date of disease progression or death from any cause. OS was measured from the initiation of the treatment or the initial diagnosis to the date of death or last follow-up. The Kaplan–Meier method was used to generate survival curves, and significant differences in the curves between the two groups

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were evaluated by the log-rank test. Multivariate regression analysis was performed using the Cox proportional hazards model. All variables with p-values <0.05 were included in the Cox model. All tests were two-sided, and differences were considered statistically significant at $p<0.05$. All statistical analyses were conducted using JMP version 11 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. Table I lists the clinical characteristics of the 62 patients who were eligible for inclusion in the study. The median age of the patients at diagnosis was 63 (range, 43-75) years. Forty-five (73%) patients were male, and 51 (82%) had a performance status (PS) of 0. The most predominant histological type was adenocarcinoma (35 patients), followed by squamous cell carcinoma (21 patients). At the time of diagnosis, 37 (60%) and 25 (40%) patients had stage IIIA and IIIB disease, respectively. All patients received CCRT containing platinum-based agents as first-line treatment. At the time of analysis, the median follow-up duration was 45 months.

Tumor shrinkage. According to tumor shrinkage, 3 (5%) patients achieved a complete response and 26 (42%) a partial response. We analyzed PFS and OS between patients who achieved a complete or partial response and those with stable disease. There were no correlations with PFS or OS in these two patient groups (median PFS: 16.5 *versus* 20.6 months, median OS: 58.4 months *versus* not reached, Figure 1).

Table I. *Patient characteristics*.

Characteristic	N=62
Age (years)	
Median (range)	63 (43-75)
Gender	
Male	45
Female	17
Smoking status	
Never-smoker	18
Smoker	44
Performance status	
0	51
1 or 2	11
Histology	
Adenocarcinoma	35
Squamous cell carcinoma	21
Others	6
Stage	
IIIA	37
IIIB	25
Pretreatment CEA	
Median (range)	7.6 (1.0-220) ng/ml
Pretreatment CYFRA	
Median (range)	3.9 (0.8-47.4) ng/ml
Response	
Complete response	3
Partial response	26
Stable disease	33
Progressive disease	0

Tumor markers. Before treatment, the median serum level of CEA was 7.6 ng/ml (range, 1.0-220 ng/ml, normal <5.0 ng/ml), and that of CYFRA was 3.9 ng/ml (range, 0.8-47.4 ng/ml, normal <3.5 ng/ml). Figure 2 shows the correlations between the levels of pretreatment tumor markers and the clinical outcomes. There was no correlation between the pretreatment serum CEA level and the survival outcome ($R^2<0.01$). Similarly, the pretreatment serum level of CYFRA was not associated with either PFS ($R^2=0.12$) or OS ($R^2=0.17$).

Furthermore, we examined the associations of normal *versus* high tumor marker levels at CCRT completion with the clinical outcome. We stratified the patients into two groups, depending on whether they had normal or high levels of the tumor markers at the time of CCRT completion. There were no differences between the groups in terms of patient characteristics such as age ($p=0.79$), sex ($p=0.78$), smoking status ($p=0.40$), PS ($p=0.52$), histology ($p=0.72$), clinical stage ($p=0.79$), and having received chemoradiotherapy (CRT) ($p=0.52$) (Table II). Fourteen patients did not receive CRT because of adverse events (n=10), undergoing surgery (n=2), a decreased PS (n=1), or progressive disease (n=1).

Univariate analysis revealed that having normal tumor marker levels at CCRT completion was significantly associated with a favorable PFS (median 54.8 months, Figure 3A), whereas none of the other factors examined was significantly associated with PFS (Table III). Multivariate analysis demonstrated that having normal levels of the tumor markers at CCRT completion was an independent and significant predictive factor for PFS (Table III).

Univariate analysis revealed that having normal tumor marker levels at CCRT completion trended towards a favorable OS (71.7 months, Figure 3B). Multivariate analysis demonstrated that normal tumor marker levels at CCRT completion was an independent and significant predictive factor for OS (Table III).

Discussion

In the present study, we examined tumor markers pre- and post-CCRT in patients with stage III NSCLC and found that patients with normal levels of tumor markers post-CCRT had a better PFS and OS compared to patients with high levels. However, pretreatment tumor markers and tumor shrinkage were not associated with PFS and OS.

Tumor biomarkers are useful for evaluating cancer in clinical practice regardless of the disease stage (17-21). Several studies have reported a relationship between high levels of pretreatment tumor markers and the clinical

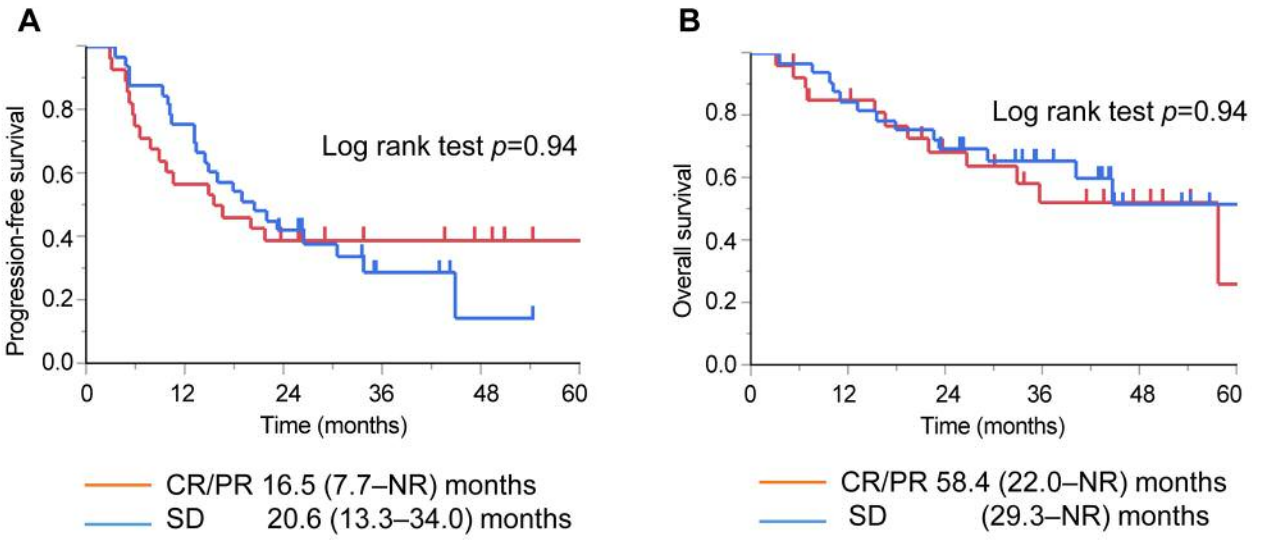

Figure 1. *Kaplan–Meier curves for progression-free survival (A) and overall survival (B) of patients with stage III NSCLC who had tumor response*.

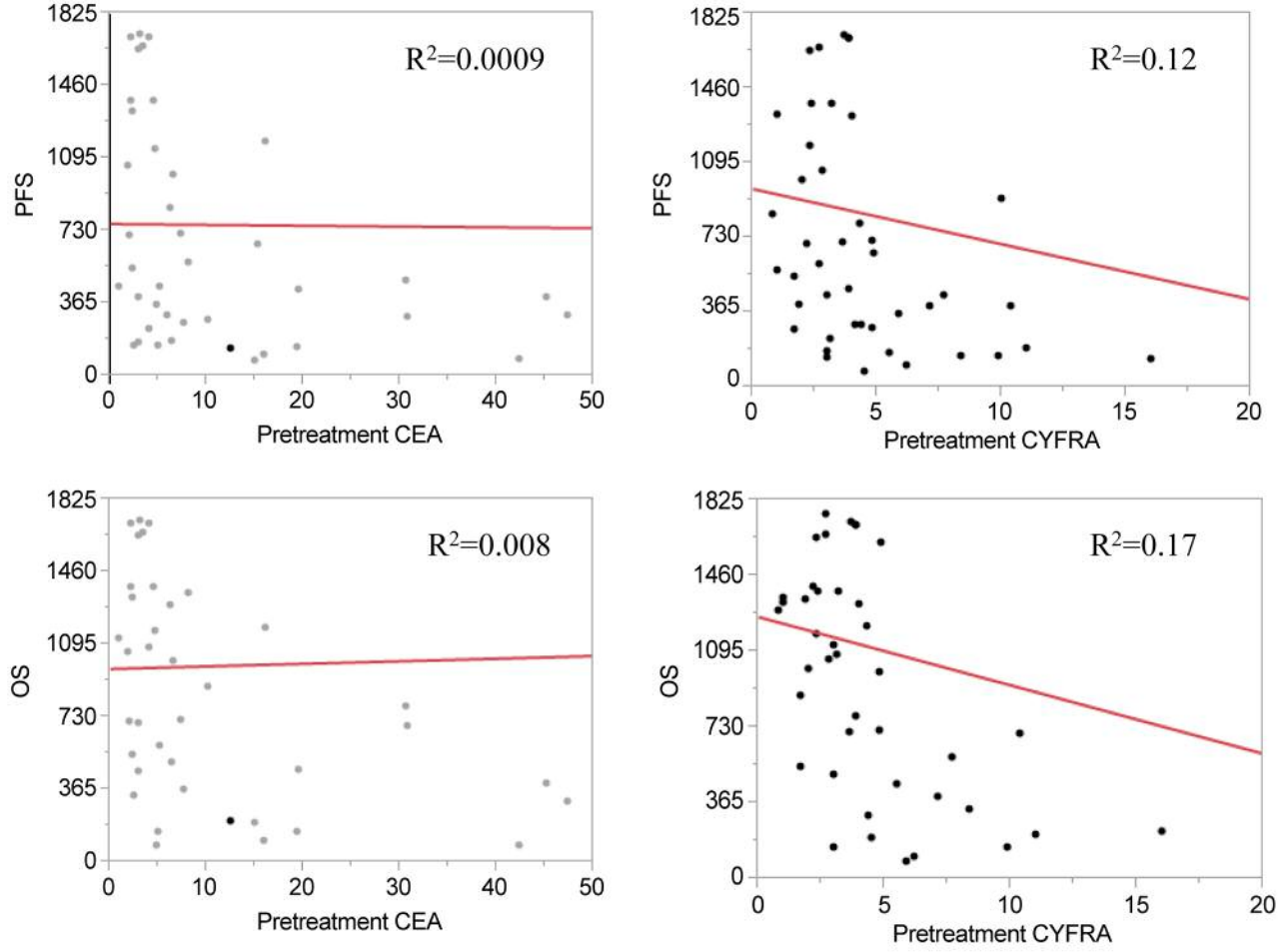

Figure 2. *Relationship between pretreatment tumor marker levels and survival*.

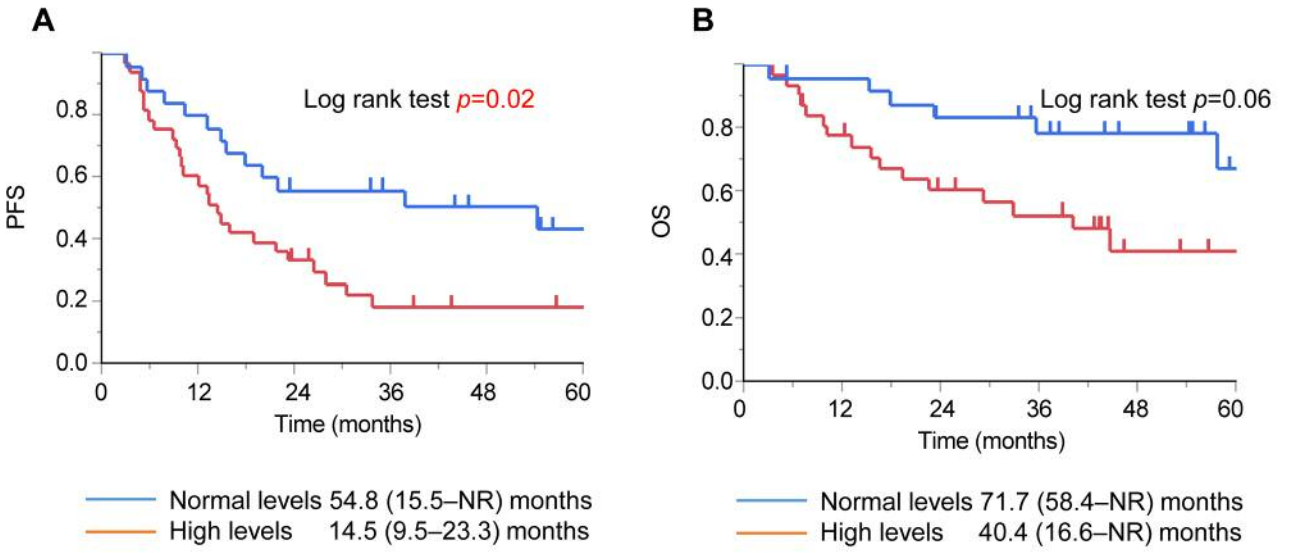

Figure 3. *Kaplan–Meier curves for progression-free survival (PFS) (A) and overall survival (OS) (B) of patients with stage III NSCLC with normal or high tumor marker levels at completion of concurrent chemoradiotherapy.*

Table II. *Patient characteristics categorized by serum tumor marker (CEA and CYFRA) levels at completion of CCRT.*

Characteristic	N	Tumor marker level at completion of CCRT		*p*-Value[a]
		Normal	High	
	58	25	33	
Age (years)				0.79
≤63		13	16	
>63		12	17	
Gender				0.78
Male		19	24	
Female		6	9	
Smoking status				0.40
Never-smoker		6	5	
Smoker		19	28	
Performance status				0.52
0		22	27	
1 or 2		3	6	
Histology				0.72
Adenocarcinoma		14	20	
Squamous cell carcinoma		7	11	
Other		4	2	
Stage				
IIIA		16	20	0.79
IIIB		9	13	
Consolidation chemotherapy				0.52
Yes		20	24	
No		5	9	

[a]Determined by Fisher's exact test. CCRT, Concurrent chemoradiotherapy.

outcome (17-20). Only one report described that a change in tumor marker levels from before treatment to 1 month after treatment using chemotherapy was significantly correlated with clinical outcome in patients with advanced NSCLC (21). Our results also indicate that normalization of tumor marker levels at CCRT completion, regardless of the pretreatment levels, is associated with better clinical outcomes in patients with stage III NSCLC.

A 5-year OS rate of 15% in stage III NSCLC patients receiving CCRT has been reported (22, 23). Akamatsu *et al.* suggested that the 2-year PFS rate may be a reliable surrogate marker for cure, instead of 5-year OS rate, in patients with stage III NSCLC treated with CCRT (24). In the present study, the 2-year PFS rate in patients with normal tumor marker levels was 56%, and the 5-year OS rate was 67% (Figure 3). In contrast, the respective rates in the group with high tumor marker levels were 33% and 41%. Therefore, normal levels of tumor markers at completion of CCRT may be a surrogate marker indicating successful CCRT treatment of stage III NSCLC.

Several investigators have demonstrated a significant association between the clinical tumor response and OS in patients with stage III NSCLC treated with CCRT (12-14). However, in the report by McAleer *et al.*, Kaplan–Meier OS curves revealed that 90% of the responders died within 4 years (12), while the study by Kim *et al.* used an insufficient follow-up (median follow-up: 16 months) (13). Furthermore, only 28 patients were eligible for enrollment in the study by Lee *et al.* (14). Our study found no relationship between tumor shrinkage and PFS or OS after

Table III. *Univariate and multivariate analyses of clinicopathological factors associated with PFS and OS.*

Factor		PFS			OS		
			Univariate	Multivariate		Univariate	Multivariate
		Median (months)	*p*-Value[a]	*p*-Value[a] HR	Median (months)	*p*-Value[a]	*p*-Value[a] HR
Age (years)							
≤63		17.7	0.85	0.57	65.3	0.99	0.81
>63		18.4		1.21	58.4		1.11
Gender							
Male	45	17.9	0.65	0.67	58.4	0.29	0.26
Female	17	18.9		0.85	71.7		1.85
Smoking							
Never-smoker	18	19.5	0.94	-	65.3	0.32	-
Smoker	44	17.2		-	NR		-
PS							
0	51	20.1	0.15	0.22	58.4	0.78	0.54
1 or 2	11	15.9		0.59	NR		1.45
Histology							
Adeno	35	21.9	0.55	-	65.3	0.26	-
Squamous	21	12.0		-	26.7		-
Other	6	26.0		-	NR		-
Tumor marker (CEA and CYFRA) level at CCRT completion							
Normal	25	54.8	0.02	0.02	71.7	0.06	0.04
High	33	14.5		0.44	40.4		0.40
CCT							
Yes	44	20.6	0.39	0.38	65.3	0.04	0.15
No	14	6.4		0.69	15.2		0.48

[a]Determined by log-rank test. PFS: Progression-free survival; OS: overall survival; CI: confidence interval; PS: performance status; Adeno: adenocarcinoma; Squamous: squamous cell carcinoma; CCRT: concurrent chemoradiotherapy; CCT: consolidation chemotherapy.

a median follow-up duration of 45 months. We consider that this may be because patients with stage III NSCLC have heterogeneous characteristics, such as tumor size, tumor invasive capacity, and number of lymph node metastases.

Our retrospective study had several limitations. First, the sample size was relatively small. Second, several confounding biases were potentially introduced in this non-randomized study. Further studies in larger cohorts are warranted.

In conclusion, we demonstrated that pretreatment tumor marker levels and tumor shrinkage were not associated with the prognosis of patients with stage III NSCLC treated with CCRT. Furthermore, we revealed that normal levels of tumor markers post-CCRT may be a useful surrogate marker indicating successful treatment of stage III NSCLC.

Conflicts of Interest

The Authors have no conflicts of interest to declare. No funding source was associated with this study.

Authors' Contributions

Study concept: Takaaki Tokito; Study design: Takaaki Tokito, Koichi Azuma; Data acquisition: Yoshiko Naito, Hiroki Natori; Quality control of data and algorithms: Norikazu Matsuo, Takashi Kinoshita; Data analysis and interpretation: Hidenobu Ishii, Kazuhiko Yamada; Statistical analysis: Tomoaki Hoshino; Manuscript preparation: Takaaki Tokito; Manuscript editing: Koichi Azuma, Kazuhiko Yamada; Manuscript review: All authors.

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References

1 Siegel R, Naishadham D and Jemal A: Cancer statistics, 2012. CA Cancer J Clin *62*: 10-29, 2012. PMID: 22237781. DOI: 10.3322/caac.20138

2 Blackstock AW and Govindan R: Definitive chemoradiation for the treatment of locally advanced non-small-cell lung cancer. J Clin Oncol *25*: 4146-4152, 2007. PMID: 17827465. DOI: 10.1200/JCO.2007.12.6581

3 Govindan R, Bogart J and Vokes EE: Locally advanced non-small cell lung cancer: The past, present, and future. J Thorac Oncol *3*: 917-928, 2008. PMID: 18670313. DOI: 10.1097/JTO.0b013e318180270b

4 Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC, Balekian AA, Diekemper R, Detterbeck FC and Arenberg DA: Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest *143*: e314S-e340S, 2013. PMID: 23649445. DOI: 10.1378/chest.12-2360

5 National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Fort Washington, PA: NCCN, 2014.

6 Segawa Y, Kiura K, Takigawa N, Kamei H, Harita S, Hiraki S, Watanabe Y, Sugimoto K, Shibayama T, Yonei T, Ueoka H, Takemoto M, Kanazawa S, Takata I, Nogami N, Hotta K, Hiraki A, Tabata M, Matsuo K and Tanimoto M: Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. J Clin Oncol *28*: 3299-3306, 2010. PMID: 20530281. DOI: 10.1200/JCO.2009.24.7577

7 Yamamoto N, Nakagawa K, Nishimura Y, Tsujino K, Satouchi M, Kudo S, Hida T, Kawahara M, Takeda K, Katakami N, Sawa T, Yokota S, Seto T, Imamura F, Saka H, Iwamoto Y, Semba H, Chiba Y, Uejima H and Fukuoka M: Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. J Clin Oncol *28*: 3739-3745, 2010. PMID: 20625120. DOI: 10.1200/JCO.2009.24.5050

8 Horinouchi H, Sekine I, Sumi M, Noda K, Goto K, Mori K and Tamura T: Long-term results of concurrent chemoradiotherapy using cisplatin and vinorelbine for stage III non-small-cell lung cancer. Cancer Sci *104*: 93-97, 2013. PMID: 23004347. DOI: 10.1111/cas.12028

9 Ohri N, Duan F, Machtay M, Gorelick JJ, Snyder BS, Alavi A, Siegel BA, Johnson DW, Bradley JD, DeNittis A and Werner-Wasik M: Pretreatment FDG-PET metrics in stage III non-small cell lung cancer: ACRIN 6668/RTOG 0235. J Natl Cancer Inst *107(4)*: djv004, 2015. PMID: 25688115. DOI: 10.1093/jnci/djv004

10 Machtay M, Duan F, Siegel BA, Snyder BS, Gorelick JJ, Reddin JS, Munden R, Johnson DW, Wilf LH, DeNittis A, Sherwin N, Cho KH, Kim SK, Videtic G, Neumann DR, Komaki R, Macapinlac H, Bradley JD and Alavi A: Prediction of survival by [^{18}F] fluorodeoxyglucose positron emission tomography in patients with locally advanced non–small-cell lung cancer undergoing definitive chemoradiation therapy: Results of the ACRIN6668/RTOG 0235 trial. J Clin Oncol *31*: 3823-3830, 2013. PMID: 24043740. DOI: 10.1200/JCO.2012.47.5947

11 Ohri N, Piperdi B, Garg MK, Bodner WR, Gucalp R, Perez-Soler R, Keller SM, Guha C: Pre-treatment FDG-PET predicts the site of in-field progression following concurrent chemoradiotherapy for stage III non-small cell lung cancer. Lung Cancer *87*: 23-27, 2015. PMID: 25468149. DOI: 10.1016/j.lungcan.2014.10.016

12 McAleer MF, Moughan J, Byhardt RW, Cox JD, Sause WT and Komaki R: Does response to induction chemotherapy predict survival for locally advanced non-small cell lung cancer? Secondary analysis of RTOG8804/8808. Int J Radiat Oncol Biol Phys *76*: 802-808, 2010. PMID: 19540055. DOI: 10.1016/j.ijrobp.2009.02.053

13 Kim DW, Shyr Y, Shaktour B, Akerley W, Johnson DH and Choy H: Long term follow up and analysis of long term survivors in patients treated with paclitaxel-based concurrent chemo/radiation therapy for locally advanced non-small cell lung cancer. Lung Cancer *50*: 235-245, 2005. PMID: 16043262. DOI: 10.1016/j.lungcan.2005.05.020

14 Lee DS, Kim YS, Kang JH, Lee SN, Kim YK, Ahn MI, Han DH, Yoo IeR, Wang YP, Park JG, Yoon SC, Jang HS and Choi BO: Clinical responses and prognostic indicators of concurrent chemoradiation for non-small cell lung cancer. Cancer Res Treat *43*: 32-41, 2011. PMID: 21509161. DOI: 10.4143/crt.2011.43.1.32

15 Kozak MM, Murphy JD, Schipper ML, Donington JS, Zhou L, Whyte RI, Shrager JB, Hoang CD, Bazan J, Maxim PG, Graves EE, Diehn M, Hara WY, Quon A, Le QT, Wakelee HA and Loo BW Jr.: Tumor volume as a potential imaging-based risk-stratification factor in trimodality therapy for locally advanced non-small cell lung cancer. J Thorac Oncol *6*: 920-926, 2011. PMID: 21774104. DOI: 10.1097/JTO.0b013e31821517db

16 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

17 Grunnet M and Sorensen JB: Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer *76*: 138-143, 2012. PMID: 22153832. DOI: 10.1016/j.lungcan.2011.11.012

18 Pujol JL, Molinier O, Ebert W, Daurès JP, Barlesi F, Buccheri G, Paesmans M, Quoix E, Moro-Sibilot D, Szturmowicz M, Bréchot JM, Muley T and Grenier J: CYFRA 21-1 is a prognostic determinant in non-small-cell lung cancer: results of a meta-analysis in 2063 patients. Br J Cancer *90*: 2097-2105, 2004. PMID: 15150567. DOI: 10.1038/sj.bjc.6601851

19 Cedrés S, Nuñez I, Longo M, Martinez P, Checa E, Torrejón D and Felip E: Serum tumor markers CEA, CYFRA21-1, and CA-125 are associated with worse prognosis in advanced non-small-cell lung cancer (NSCLC). Clin Lung Cancer *12*: 172-179, 2011. PMID: 21663860. DOI: 10.1016/j.cllc.2011.03.019

20 Jung M, Kim S.H, Hong S, Kang YA, Kim SK, Chang J, Rha SY, Kim JH, Kim DJ and Cho BC: Prognostic and predictive value of carcinoembryonic antigen and cytokeratin-19 fragments levels in advanced non-small cell lung cancer patients treated with gefitinib or erlotinib. Yonsei Med J *53*: 931-939, 2012. PMID: 22869475. DOI: 10.3349/ymj.2012.53.5.931

21 Facchinetti F, Aldigeri R, Aloe R, Bortesi B, Ardizzoni A and Tiseo M: CEA serum level as early predictive marker of outcome during EGFR-TKI therapy in advanced NSCLC patients. Tumour Biol *36*: 5943-5951, 2015. PMID: 25731731. DOI: 10.1007/s13277-015-3269-6

22 Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC, Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S and Pignon JP: Meta-analysis of

concomitant *versus* sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol *28*: 2181-2190, 2010. PMID: 20351327. DOI: 10.1200/JCO.2009.26.2543

23 Ahn JS, Ahn YC, Kim JH, Lee CG, Cho EK, Lee KC, Chen M, Kim DW, Kim HK, Min YJ, Kang JH, Choi JH, Kim SW, Zhu G, Wu YL, Kim SR, Lee KH, Song HS, Choi YL, Sun JM, Jung SH, Ahn MJ and Park K: Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. J Clin Oncol *33*: 2660-2666, 2015. PMID: 26150444. DOI: 10.1200/JCO.2014.60.0130

24 Akamatsu H, Mori K, Naito T, Imai H, Ono A, Shukuya T, Taira T, Kenmotsu H, Murakami H, Endo M, Harada H, Takahashi T and Yamamoto N: Progression-free survival at 2 years is a reliable surrogate marker for the 5-year survival rate in patients with locally advanced non-small cell lung cancer treated with chemoradiotherapy. BMC Cancer *14*: 18, 2014. PMID: 24422706. DOI: 10.1186/1471-2407-14-18

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